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Cognitive impairment in COPD: an often overlooked co-morbidity.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a disease of multiple co-morbidities, such as lung cancer, coronary artery disease and osteoporosis [1]. Co-morbid neurocognitive damage and dysfunction is frequently overlooked despite a growing body of well conducted cross sectional and longitudinal studies pointing to a frequent and important association. A diagnosis of mild cognitive impairment (MCI); when deficits develop in cognitive domains, is important since it is known to worsen outcomes and increase healthcare burden in COPD [2]. MCI has 5-10% annual conversion rate to dementia, but crucially is considered a potentially reversible state [3]. It is therefore an urgent public health priority to clarify risk factors for MCI. Although epidemiological research suggests that COPD increases the risk of cognitive impairment, establishing causality is challenging. Various pathological mechanisms are hypothesised including hypoxia and structural brain changes. In this expert opinion we will discuss evidence for the association of COPD and cognitive impairment, possible underlying mechanisms, the impact on morbidity and mortality, and suggest how future research could help us understand and manage this common co-morbidity.

2. Epidemiological evidence linking COPD and cognitive impairment

Most observational epidemiological research suggests COPD is associated with an increased risk of cognitive impairment, although estimates vary. A literature review including 17 studies estimated a prevalence of cognitive dysfunction ranging from 10-61% in COPD [3]. A systematic review found 8 of 12 studies reviewed reported increasing cognitive dysfunction with worsening COPD severity [4]. Longitudinal work has demonstrated that COPD can influence the risk of developing MCI. A large retrospective observational cohort study showed midlife obstructive lung disease was associated with increased risk of developing of Alzheimer's or MCI Odd Ratio (OR) 1.33 (95% CI, 1.07-1.64) [5].

The pattern of cognitive impairment has been studied, with evidence of a global impairment in some groups, whilst others show a COPD specific pattern of deficits in attention, memory, learning and motor functions[3]. As the extent and pattern of cognitive deficits vary, multiple psychometric tests are required for full evaluation in research and clinical practice [6].

Methodological errors may be contributing to mixed results. Observational studies often lack a matched smoking control group, despite smoking being an important risk factor for cognitive impairment. Case control studies are often limited by small numbers of participants weakening power. Cohort studies often rely on health care records for diagnoses of COPD and cognitive impairment, which may be inaccurate. Meta-analyses are not always possible due to differing definitions and tests of cognitive impairment, heterogenous sample populations, and poor outcome definitions (MCI and dementia are often merged).

3. Hypothesis for mechanism linking COPD and cognitive impairment

The exact aetiological link between COPD and cognitive impairment remains unknown. Proposed casual mechanisms include hypoxia mediated neuronal damage or reduction in neurotransmitters that require oxygen-dependent enzymes for synthesis. A meta-analysis of nine studies found a negative correlation between PaO_2 and cognitive function with a pooled $r = 0.405$, 95% CI 0.31-0.55, but with sizeable heterogeneity, so the impact of hypoxia mechanism remains uncertain [7]. Hypoxia cannot be the sole mediator as cognitive deficits have been found in both hypoxic and non-hypoxaemic patients. Acute oxygen therapy doesn't impact cognitive function [8], and whilst long term oxygen has been shown to improve cognition, it is dependent on which cognitive test is being used [9]. Therefore, although hypoxia may explain some cognitive deficit, other factors are also important. The relationship with carbon dioxide is even less clear with some studies showing a relationship with executive function, attention and verbal memory with others showing no relationship [10].

Vascular brain disease is a common comorbidity in COPD, as identified in up to 50% of inpatients [3]. Several plausible mechanisms for vascular disease in COPD have been suggested including systemic inflammation, oxidative and physiological stress [11]. The pattern of vascular brain disease seen in COPD appears to differ from that of ischaemic cerebrovascular disease and vascular dementia. Microvascular disease is increased in COPD patients compared to smoking controls, as demonstrated by significant arteriole and venous dilation in retinal images. These changes are associated with lung function independent of standard cardiovascular risk factors [12]. Neuroimaging has revealed grey matter atrophy in COPD patients that cannot be explained by cardiovascular risk and smoking alone. Cerebral white matter lesions (a marker of cerebrovascular pathology) are seen, but may lead to anxiety and depression rather than significant cognitive impairment [13]. Functional and diffusion MRI has shown widespread disturbance in activity of grey matter, and reduced white matter integrity throughout the brain [14]. Brain networks in those with COPD show more evidence of damage than in controls, but this does not appear sufficient to reduce the networks' efficiency, and direct relationships with cognitive measures have not been found [15].

It is important to consider smoking since it increases the risk of both COPD and vascular brain disease. For example, smokers MRI's reveal increased periventricular white matter hyperintensities. The effect may be dose dependent with greater pack/years associated with greater brain atrophy, larger sulcal and ventricle volumes [16]. Smoking does not explain all the risk of vascular brain disease and cognitive impairment. Even adjustment for smoking, lung function remains associated with white matter brain lesions, with a 'dose response' like relationship between severity of lung function deficit and risk of cognitive impairment [17,18].

During acute exacerbations patients with COPD have greater cognitive impairment than similar patients with acute heart failure [19]. This acute cognitive deterioration is seen to improve over six weeks in most, but not in all patients [20]. Whether exacerbations change cognition in the long term is unclear.

Physical activity may positively impact cognition in patients with COPD. Proposed mechanisms include decreasing oxidative stress, reducing systemic inflammation and improving microvascular circulation [21]. Reduced mobility can contribute to social isolation, anxiety and depression potentially contributing to progressive cognitive impairment. Exercise programs to improve cognition have been studied, however a meta-analysis of trials is not possible due to heterogeneity of studies, typifying research issues in this field [22]. It remains uncertain if pulmonary rehabilitation and exercise classes will improve cognition.

4. Impact of cognitive impairment in COPD

Whilst efforts to fully understand the causal and aetiological relationship between COPD and cognition is ongoing, the impact on morbidity is clear. Impairment in memory, cognitive flexibility and visual processing may have direct impact on COPD patients' ability to self-manage their disease [6]. Studies have shown greater disability, risk of exacerbation, and poorer medication compliance in those with cognitive impairment [2,10,23]. The effect of cognitive impairment on mortality in COPD is less certain. Cognitive dysfunction is associated with increased mortality in acute hospital admissions even in those without COPD, but its effect specifically in the COPD population has not been well studied and available results are mixed [10]. A large prospective study in COPD found no link between mortality and Mini Mental State Examination (MMSE), whilst another study found drawing impairment was a risk factor for mortality in those with severe COPD [10,24].

5. 5 Year View

Despite decades of research, our understanding of cognitive impairment in COPD remains incomplete. Most studies are in small populations, often repeating previous study methodologies but with different cognitive tests. Other studies examine narrow putative pathological processes, even though we are yet to ascertain if COPD directly causes increased risk of cognitive impairment.

Given the significant shared risk factors, even after adjustment for confounders, traditional observational studies will not determine causality. Novel epidemiological techniques to infer causality such as Mendelian Randomization offer the opportunity to explore this important gap in our knowledge.

Our understanding of COPD pathogenesis is evolving, which in turn should change the way that we think about the relationship between COPD and its co-morbidities. It is becoming clear that COPD and lung function decline is not simply due to smoking, but early life factors significantly affect lung development and lung function trajectories. Available data points to a link between impaired lung function and cardiovascular co-morbidity as early as the third decade [25]. More work is needed to see when, and to what extent, cognitive deficits are associated with these trajectories.

Large consortiums and birth cohorts will provide bigger, longitudinal samples to facilitate more powerful epidemiological research, Mendelian Randomization studies and trajectory analysis in well phenotyped cohorts.

6. Summary

Whilst it remains unclear if COPD *causes* cognitive impairment, and what the underlying mechanisms could be, there is an association between COPD and cognition which is harmful to an already vulnerable population. Too often observational analysis of prevalence and underlying mechanism are being repeated, with varying cognitive tests in small heterogenous populations preventing meta-analysis and definitive conclusions. We welcome research designed to evaluate causality of the relationship and suggest use of Mendelian Randomization. However, if the association is not causal and the result of shared environmental, genetic or behavioural processes it is important to not overlook the impact of impaired cognition on people living with COPD. Research to discover pharmacological and non-pharmacological interventions to manage cognitive impairment in both acute and stable COPD patients should also be prioritised.

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